



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|--|-------------|----------------------|--------------------------|------------------------|
| 10/661,097 | 09/12/2003 | Andrew Vaillant | 16051-6US | 6581 |
| 20988 7590 01/13/2009 OGILVY RENAULT LLP 1981 MCGILL COLLEGE AVENUE SUITE 1600 MONTREAL, QC H3A2Y3 CANADA | | | | |
| | | | EXAMINER ZARA, JANE J | |
| | | | ART UNIT 1635 | PAPER NUMBER |
| | | | MAIL DATE 01/13/2009 | DELIVERY MODE PAPER |

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/661,097

Applicant(s)

VAILLANT ET AL.

Examiner

Jane Zara

Art Unit

1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 07 July 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1, 2, 15, 17, 18, 21, 27 and 40-42 is/are pending in the application.
- 4a) Of the above claim(s) 40 and 41 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1, 2, 15, 17, 18, 21, 27, 42 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

This Office action is in response to the communications filed 7-7-08.

Claims 1, 2, 15, 17, 18, 21, 27, 40-42 are pending in the instant application.

Election/Restrictions

This application contains claims 40, 41, and SEQ ID Nos. other than SEQ ID NO. 24, drawn to an invention nonelected with traverse in the reply filed on 12-20-07. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

The declaration under 37 CFR 1.132 filed 7-7-08 is insufficient to overcome the rejections based upon 35 U.S.C. 112, first paragraph, as set forth in the last Office action because for the reasons set forth below.

Applicant argues and states in the declaration filed 7-7-08 that

Response to Arguments and Amendments

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

Maintained Rejections

Claims 1, 2, 15, 17, 18, 21, 22, and 27 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for the reasons of record set forth in the Office action mailed 3-6-08 and for the reasons set forth below.

Applicant's arguments and declaration filed 7-7-08 have been fully considered but they are not persuasive. Applicant argues that adequate description has been provided for the broad genus of compounds claimed. Applicant argues that the claims have been amended to recite the limitations that the anti-viral activity of the oligonucleotides occur principally by a sequence independent mode of action and the oligonucleotides now comprise all phosphorothioated internucleotide linkages, and the genus' common features are therefore clarified. Applicant also argues that the antiviral activity occurs due to the presence of phosphorothioate linkages.

The claims are drawn to methods for the prophylaxis and/or treatment of HSV-1, HSV-2 and CMV infection in a subject comprising the administration of any oligonucleotide at least 30 nucleotides in length, which is optionally double or single-stranded, which provides anti-viral activity by a non-sequence complementary mode of action, and which is non-sequence complementary to the target virus' nucleic acid sequences, and which oligonucleotide optionally comprises all phosphorothioated internucleotide linkages, and does not comprise a TG-rich sequence, and inhibits either virus absorption or virus infection into the cell.

Contrary to Applicant's assertions, the specification and claims do not adequately describe the distinguishing features or attributes concisely shared by the members of the genus comprising oligonucleotides with "non-sequence complementary" modes of action and comprising any random sequences, whereby prevention and treatment of HSV-1, HSV-2 or CMV is obtained in an organism. It is unclear what is embraced by anti-viral activity occurring principally by a "non-sequence complementary mode of

action," and how this can be determined if random sequences are used. How, for instance, can aptamers be ruled out as a means of inhibition? Aptamers, after all, recognize the higher order structure imparted by a nucleic acid molecule, and are therefore not sequence independent in their mode of action. It is therefore unclear how one can determine with certainty how any randomer sequence is acting in a sequence independent manner.

It is also unclear why some oligonucleotides that have been labeled randomers have specific sequences disclosed, while others are simply referred to as "NNNNN..." (compare REP 2006, 2018, and 2031) in Table 1 of the specification. How can the mode of action be definitively determined if the biological responses vary so widely between the oligonucleotides broadly claimed, especially without full disclosure of each of the sequences of the oligonucleotides utilized and compared?

Another point of confusion in satisfying the written description requirement arises from the new amendments filed, which now narrow the genus of oligonucleotides to those excluding TG-rich regions. A reading of paragraph 0063 of the instant disclosure states that the oligonucleotides of the instant claims do **not** consist essentially of polyA, polyC, polyG, polyT, Gquartet, or a TG-rich sequence, yet the arguments and declaration filed on 7-7-08 both stress the success of REP 2031 in vivo, and this oligonucleotide consists of a polyC 40mer. Are these limitations recited in the specification also included in determining what is encompassed by the instantly claimed genus of compounds? If so, it is unclear why Applicant has ignored these limitations in

arguing that the genus of compounds provided treatment effects now includes a polyC oligonucleotide.

The specification teaches rather large differences in the abilities of various randomers to inhibit different viral infections, and each randomer is tested empirically because no concise description of common characteristics for this expansive genus has been provided. The disclosure of five effective oligonucleotides found to reduce or prevent viral infectivity of some strains of virus, with no common features, physical characteristics, or modes of action described or purportedly shared between them, do not provide adequate description for the very large genus of oligonucleotides claimed, especially in light of the limitations recited in paragraph 0063 of the specification, which would preclude inclusion of REP 2031, SEQ ID NOs. 20, 23 as claimed in withdrawn claim 40. The concise structural features encompassed by the instantly claimed genus, especially in light of the teachings of the original specification, are therefore unclear and contradictory.

The instant disclosure and declarations filed October 5, 2006 and July 7, 2008 do not clarify what common attributes, if any, are encompassed by this very broad genus. Concise structural features that would distinguish structures within the broadly claimed genus from those outside the genus, in light of the teachings of the specification as originally filed, are missing from the disclosure, and without empirically testing each candidate oligomer, it is unclear which of these species would provide for the functions claimed, the ability to prevent or inhibit viral infections, including the instantly claimed HSV-1, HSV-2 and/or CMV infections in a subject.

For these reasons, the very broad large genus claimed was not adequately described at the time of filing by Applicant.

Claims 1, 2, 15, 17, 18, 21, 22, and 27 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement for the reasons of record set forth in the Office action mailed 3-6-08 as for the reasons set forth below.

Applicant's arguments and declaration filed 7-7-08 have been fully considered but they are not persuasive. Applicant argues the full scope of invention is enabled.

The claims are drawn to methods for the prophylaxis and/or treatment of HSV-1, HSV-2 and CMV infection in a subject comprising the administration of any oligonucleotide at least 30 nucleotides in length, which is optionally double or single-stranded, which provides anti-viral activity by a non-sequence complementary mode of action, and which is non-sequence complementary to the target virus' nucleic acid sequences, and which oligonucleotide optionally comprises all phosphorothioated internucleotide linkages, and does not comprise a TG-rich sequence, and inhibits either virus absorption or virus infection into the cell.

The declaration filed on 7-7-08 states that the oligonucleotides rapidly lost inhibitory activity when added at increasingly longer times after infection, and had little effect when added 60 minutes or later after infection on viral activity, lending credence to the fact that the oligonucleotides act at least during the adsorption or cell entry phase of the host cell by the virus. The critical timing of inhibition by the oligonucleotides requires that adequate quantities be available to the host cell that is about to be

infected. The ability to provide these necessary quantities to vulnerable host cells in vivo, which are about to become infected with the virus, and to provide adequate quantities within this crucial timeframe to appropriate host cells requires undue experimentation beyond that provided in the instant specification. In vitro inhibition is not representative of in vivo efficacy for the broad genus of compounds claimed.

Applicant argues that the three species of oligonucleotides disclosed in the instant specification, and two oligonucleotides provided in the Declaration filed October 5, 2006, which were found to provide treatment and prophylactic effects in an appropriate animal model, indeed provide adequate description for the very large genus comprising any oligonucleotide at least 30 nucleotides in length which provides anti-viral activity by a "non-sequence complementary mode of action," and which is "non-sequence complementary" (*e.g.*, to a viral gene).

Applicant argues that the full scope of the claims is enabled because the instant disclosure disclose various oligonucleotides with different lengths used to identify their efficacy as potential anti- HSV-2 molecules, and that the inhibitory activity is attributable to the fully phosphorothioated internucleotide linkages. In addition, according to Applicant, in vivo efficacy has been shown for three oligonucleotides - two oligonucleotides (REP 2006 and 2031) were found to prevent HSV-2 transmission in a mouse model, and three oligonucleotides (REP 2006, 2031 and 2107) reduced CMV liver titers upon intraperitoneal administration in a mouse model.

The specification teaches the in vitro inhibition of HSV-2 using oligonucleotides which are partially complementary to a target HSV-2 gene sequence. These

experiments, however, are not representative of providing in vivo treatment or prophylaxis using a representative number of species of the expansive genus of nucleic acid molecules claimed.

Applicant is correct that in vivo efficacy has been shown for the particularly described oligonucleotides, REP 2006, 2031 and 2107, regarding their ability to prevent or reduce HSV-2 or CMV infections in appropriate animal models as indicated in the declaration. The instant application therefore appears to be enabled for the ability to treat CMV upon systemic administration of REP 2006, 2031 and 2107, and for the ability to treat or prevent HSV-2 infection upon administration of REP 2006 and 2031.

The full scope of the claims, however, drawn to methods for the prevention and treatment of HSV-1, -2, and CMV comprising administration of any (random) oligonucleotide at least 30 nucleotides in length with anti-viral activity occurring by any non-sequence complementary mode of action, and which are fully phosphorothioated, is not enabled.

The ability to predict a particular randomer's ability to treat or prevent a viral infection in a subject is a highly unpredictable endeavor. The ability of three oligonucleotides to provide treatment effects of CMV and of two oligonucleotides to provide treatment or prophylactic effects for HSV-2 is not correlative or representative of the ability to predict the efficacy of any oligonucleotide of at least 30 nucleotides and with fully phosphorothioated internucleotide linkages, acting in any non-complementary mode, to provide such prophylactic effects in a subject. This requires experimentation beyond that provided in the instant specification.

For these reasons, the instant rejection is maintained.

New Objections and Rejections/ Necessitated by Amendment

Claim Objections

Claims 1, 2, and 15 are objected to because of the following informalities: In claim 1, line 8, claim 2, line 7, claim 15, line 8, the word "comprises" is grammatically incompatible with the verb "does" which precedes it. Appropriate correction is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 15, 17, 18, 21, and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lin et al (USPN 6,849,610) in view of McKay et al (USPN 6,133,246) insofar as the claims are drawn to a method of treatment of HSV-1, HSV-2 or CMV infection in a subject comprising the administration of an oligonucleotide at least 30 nucleotides in length, which is optionally double stranded, wherein the anti-viral activity occurs by a non-sequence complementary mode of action, and which oligonucleotide further comprises all phosphorothioate linkages, does not comprise a TC-rich sequence, and optionally further comprises one other chemical modification, which is optionally a 2' modification to the ribose moiety.

Lin et al (USPN 6,849,610) teach a method of treatment of HSV-1, HSV-2 or CMV infection in a subject comprising the administration of an oligonucleotide at least 30 nucleotides in length, which is optionally double stranded, wherein the anti-viral activity occurs by a non-sequence complementary mode of action, and which oligonucleotide further comprises modified internucleotide linkages, does not comprise a TC-rich sequence, and optionally further comprises one other chemical modification, which is optionally a 2' modification to the ribose moiety (see entire document, esp. col. 1-8, 11, 12, 14, claims 1-8).

Lin does not teach specifically teach fully phosphorothioated internucleotide linkages as modified internucleotide linkages.

McKay et al (USPN 6,133,246) teach the incorporation of phosphorothioates, methyl phosphonates and 2'-O-sugar modifications for enhancing oligonucleotide stability (see esp. col. 9-10).

It would have been obvious to one of ordinary skill in the art to utilize random sequences for inhibiting viral infection in a subject because Lin teaches the inhibition of viral adhesion and infectivity using oligonucleotides of random sequences as instantly claimed. One of ordinary skill in the art would have been motivated to incorporate the well known modifications of phosphorothioates, methyl phosphonates and 2'-O-sugar modifications into oligonucleotides because the technology to do so was well known in the art at the time of the instant invention, and McKay teaches the advantages of incorporating these modifications into oligonucleotides for enhancing binding properties, cellular uptake, and oligonucleotide stability. One of ordinary skill in the art would have been motivated to generate a fully phosphorothioated oligonucleotide to enhance stability and cell entry because the benefits of phosphorothioates were well known in the art at the time of filing and the technology to replace all of the internucleotide linkages was well known in the art and would have required routine experimentation at the time of filing, and to do so would have been a design choice using routine experimentation. One of ordinary skill in the art would have reasonably expected that fully phosphorothioated linkages would contribute to cellular uptake and oligonucleotide stability, relying on the teachings of both McKay and Lin.

For these reasons, the instant invention would have been obvious to one of ordinary skill in the art at the time the invention was made.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the

unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 42 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 2 of U.S. Patent No. 7,358,068. Although the conflicting claims are not identical, they are not patentably distinct from each other because both claims are drawn to methods of treatment of viral infections in a subject comprising administration of SEQ ID NO. 24 comprising phosphorothioated internucleotide linkages, wherein antiviral activity occurs principally by a sequence independent mode of action.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94

(December 28, 1993) (see 37 C.F.R. ' 1.6(d)). The official fax telephone number for the Group is 571-273-8300. NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jane Zara whose telephone number is (571) 272-0765. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Douglas Schultz, can be reached on (571) 272-0763. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jane Zara
1-9-09

/Jane Zara/

Primary Examiner, Art Unit 1635

